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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/807,510	03/24/2004	Tao Lu Lowe	059516-0058	3378

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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/807,510	LOWE ET AL.	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-24* is/are pending in the application.

4a) Of the above claim(s) *7 and 10-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8,9 and 16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of request for extension of time, declaration under 37 CFR 1.132, request for reconsideration and remarks filed 6/10/09. No claim is amended. Claim 3 is canceled. Claims 1, 2 and 4-24 are pending. Claims 7 and 10-15 are withdrawn from consideration.

Response to Arguments

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 2, 4-6, 8, 9 and 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hennink et al. (WO 98/00170) in view of Park et al. (US 6,271,278) or Hennink et al. (US 6,303,148) for reasons of record.

4. Hennink (WO 98/00170) describes a hydrolysable hydrogels for controlled release of drugs such as protein drugs (abstract; page 1, lines 22-33; page 12, lines 14-31) with the hydrogel composition for the delivery of the protein drug meeting claims 16-19. The administration of the composition comprising the hydrolysable hydrogel polymer and the protein drugs to human (page 2, lines 4-19; page 3, line 30; page 5, lines 28 and 29; page 6, lines 7 and 8; and page 13, lines 9-19) meets the limitations of claims 20 and 21. The drugs in Henning are loaded into the hydrogel in an aqueous solution (page 4, lines 15-23; page 6, line 2) meeting claim 23. The hydrolysable polymer of Hennink has polyglycolic acid and or polylactic acid spacers between mathacrylate type polymer and dextran (page 7, lines 24-36; pages 8; Examples 2, 3 and 4); the lactide or glycolide meets claim 4; the dextran meets claim 5 and the triblock polymer meets the generic polymer of claim 1 having the biodegradable segment, lactic acid and dextran and the smart segment, HEMA. Furthermore, the hydrogel composition is prepared in the form of microspheres (page 3, line 7; page 10, lines 26-34; page 12, line 7; page13, line 21) meeting claim 8. Claims 2 and 9 recite the properties of the polymer.

For claims 22 and 24, the artisan would have good reason to administer the composition having the appropriate concentration of the drug with the expectation that the delivery of the desired amounts of the drug would be released to effect the desired result. Hennink's (WO 98/00170) polymer does not have the smart polymer segment listed in the amended claim 1, that is polymers such as poly(N-isopropylacrylamide), poly(N-alkylacrylamide), poly(N-n-

propylacrylamide), poly(N-isopropylmethacrylamide), poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) and elastin-like polypeptides.

But Park describes "smart" or "intelligent" hydrogels (column 33, line 14) formed from N-isopropylacrylamide olefinic monomers cross-linking particles of dis-integrants such as dextran sulfate (column 6, lines 7-10, 31, 35-42, 52, 56) for sustained/controlled delivery of drugs (column 30, line 10).

Also, Hennink (US 6,303,148) discloses polymers comprised of sensitive polymer such as poly-N-isopropylacrylamide grafted onto dextran for controlled release of drugs such as protein drugs (column 1, line 16; column 5, lines 35-44).

Therefore, taking the general teachings of the Hennink (WO 98/00170) in view of Park or Hennink (US 6,303,148), one having ordinary skill in the art would have reasonable expectation of success that using poly N-isopropylacrylamide in place of HEMA would produce a polymer that would be effective in sustained delivery of drugs such as protein drugs.

Response to Arguments

5. Applicant's arguments filed 06/10/09 have been fully considered but they are not persuasive as the arguments apply to the present rejections.

6. Applicant argues that it would not have been obvious to use the poly N-isopropylacrylamide of Park or Hennink '148 in place of the HEMA of Hennink '170 because the configuration recited in claim 1 achieves unexpected improved results as stated by the Lowe declaration under 37 CFR 1.132. Applicant further refers to the Lowe declaration that points Fig. 10 of the instant disclosure that shows that BSA having molecular weight of 69.4 kDa was released from NIPAAm-Dextran derivative at 37 °C in "over 15 days," while Fig. 5 of Hennink

'170 shows that "IgG having molecular weight of 150 kDa, a much larger molecule, was released from the HEMA polymer of Hennink '170 for a maximum release time of 6 days. So that, applicant argues that, the ordinary skilled artisan, which Dr. Lowe is at the time the invention was made, would have expected to have longer release rate for larger molecule than for smaller molecule.

7. The examiner disagrees with the applicant that the ordinary skilled artisan would have expected the release rate of biological molecules from dextran hydrogels to be based solely on the molecular weight or the size of the molecule from dextran hydrogels using Fig. 5 of Hennink that showed that IgG was released from the dextran hydrogel within 6 days and calling the data in instant Fig. 10 unexpected in that BSA, a smaller molecule than IgG was released within 15 days or longer. Applicant's argument for expecting longer release rates for larger molecules and shorter release rates for smaller molecules from dextran hydrogels does not present the whole picture and applicant has not considered the Hennink reference as a whole in view of the reasoning that follows: Hennink provides the following teachings that would guide the ordinary skilled artisan at the time the invention was made regarding release of protein drugs from dextran hydrogels:

a) Hennink teaches that the release of a compound from dextran hydrogel can be controlled by adjusting the water content and/or the degree of cross-linking, the degree of substitution, the number and length of hydrolysable groups in the spacer, the choice of hydrolysable spacers of dextran hydrogels (see page 7, lines 5-9 ; page 11, lines 24-35 of Hennink). Specifically, lines 31-35 state that glycolic acid based spacers are hydrolytically more sensitive than spacers based on lactic acids.

b) Hennink teaches that one can obtain dissolution times of from about 1 day to about 3 months or longer by varying the initial water content and the DS of the hydrogel (see page 10, lines 1-11 of Hennink).

c) Hennink teaches that the manner in which the macromolecule is loaded on to the gel influences the loading capacity and hence the release profile. For example, burst release is obtained when the macromolecule adheres to the outside surface of the hydrogel (see page 10, lines 18-25 of Hennink).

d) Hennink teaches that the rate of release depends on the size of the hydrogel particles (see page 12, lines 4-7 of Hennink).

e) That Contrary to hydrogel system, the rate of release from dextran hydrogels does not depend on the length of the water soluble polymers (see page 12, lines 8-12 of Hennink).

8. Thus, taken the teaching of Hennink as a whole, it can be seen as enumerated in at least from a)-e), that the rate of release of molecules from a dextran hydrogel can be tailored to provide first or zero order release (see page 11, lines 14-35 of Hennink). Therefore, at the time the invention was made, the ordinary skilled artisan would not have expected that the release of compounds from dextran hydrogel would depend solely on the molecular weight of the compound, which is supported by Hennink that the hydrogel can be easily tailored "with respect to protein drug release kinetics" ((see page 9, lines 24-30 of Hennink).

9. Therefore, it is not persuasive to arrive at a conclusion that the ordinary skilled artisan would have expected a longer release rate for larger molecule than smaller molecule based on Hennink. Furthermore, the comparison between Fig. 5 of Hennink and instant Fig. 10 has not considered the degree of substitution and the water content of the hydrogels. The composition

used in instant Fig. 10 is not commensurate in scope with the polymer in claim 1. See page 5, paragraph [020] of the instant specification stating that the BSA is released from NIPAAM-co-DEX-lactataHEMA, which is not the claimed polymer in claim 1.

10. Applicant also argues that the claimed polymeric material shows a sustained swelling ratio for up to 8 months according to instant Fig. 3 while the HEMA polymer disclosed in Hennink '170 shows a rapid drop in swelling ratio after less than 22 months according to Fig. 4 of Hennink.

11. The examiner disagrees with applicant's comparison. The polymer of claim 1 is generic and the polymer in instant Fig. 3 cannot be generic because, in order to form a specific polymer that produces the observed swelling ratio. Furthermore, Fig. 3 has ratios of PNIPAAM, PLLA and DEX while the polymer in claim 1 does not have any ratios. Also, Fig. 3 is representation of a polymer having PNIPAAM, PLLA and DEX having the specified ratios, while the smart segment in claim 1 is any of poly(N-isopropylacrylamide), poly(N- alkylacrylamide), poly(N-n-propylacrylamide), poly(N-isopropylmethacrylamide), poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide), or elastin-like polypeptide so that Fig. 3 represents one polymer out of the many polymers in claim 1. While swelling ratio is a property that would be characteristic to a specific polymer that is completely defined by the amounts of the components, the claims have not recited any specific polymer and swelling ratios. Therefore, the polymer in Fig. 3 is not the claimed polymer and the polymer composition giving rise to the data of Fig. 3 is not commensurate in scope with the claimed polymer.

12. Therefore, claim 1 and claims dependent from claim 1 are rendered obvious by Hennink in view of Park or Hennink '148.

13. Claims 1, 2, 4-6, 8, 9 are 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bos et al., "Hydrogels for the Controlled Release of Pharmaceutical Proteins," in Pharmaceutical Technology, October, 2001, pp 110, 112, 114, 116, 118, 120 for reasons of record.

14. Bos describes hydrogel for delivery of proteins listed under candidate proteins on page 110. The hydrogel is formulated from natural materials, synthetic polymers and responsive polymers (see list under hydrogel material on page 112) and listed under responsive polymers are methacrylates and poly(n-isopropylacrylamide). Claim 2 described the inherent characteristic/properties of the polymeric material of claim 1. The polymeric material of Bos microsphere (see pages 116, 118) meeting claim 8. The protein pharmaceutical meets claims 16-19. Bos contemplates administering the hydrogel composition so that claim 20 is met and because candidate protein such as erythropoietin, IL-2 and the rest of the candidate proteins are suitable for administration to human, claims 21 and 22 are also rendered obvious. The polymer and the candidate proteins are mixed to form the hydrogel composition (see the pages 110, 112, 114) meeting claims 23 and 24. Bos specifically mentions modified hydrogels comprised of dex-lactate-HEMA (page 114) and for hydrogel of that nature, dextran meets the hydrophilic segment of claims 1, 6; the lactate meets the hydrophobic segment of claims 1, 4; the HEMA meets the smart segment of claim 1, 9 except that the smart segment of claim 1 is poly(N-isopropylacrylamide), poly(N-alkylacrylamide), poly(N-n-propylacrylamide), poly(N-isopropylmethacrylamide), poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) or elastin-like polypeptides. But, in Bos poly(n-isopropylacrylamide) and methacrylates are listed as responsive polymers (page 112, under hydrogel materials and also under abbreviations) with

HEMA being a methacrylate. Thus, taking the teaching of Bos, one having ordinary skill in the art at the time the invention was made would have reasonable expectation that using poly(n-isopropylacrylamide) in place of the HEMA in the dex-lactate-HEMA would produce a hydrogel that would provide the desired controlled release of the protein pharmaceuticals.

Response to Arguments

15. Applicant's arguments filed 06/10/09 have been fully considered but they are not persuasive.

16. Applicant argues that because the claimed polymer has been shown to achieve unexpected results according to the declaration of Dr. Lowe, it would not have been obvious to a person of ordinary skill in the art, based on the disclosure of Bos, to achieve the polymeric composition of claim 1.

17. The examiner disagrees. The composition showing the unexpected results in Fig. 3 and of the instant application is not the composition of claim 1 and as such the composition used in Fig. 3 is not commensurate in scope with claim 1. It is noted that paragraphs 3, 5 and 6 of the declaration by Dr. Lowe specifically refers to Hennink. With regards to Bos and HEMA, it is noted that Bos specifically identifies poly(n-isopropylacrylamide) and methacrylates as responsive polymers (page 112, under hydrogel materials and also under abbreviations) with HEMA being a methacrylate. Thus, while Bos specifically mentions modified hydrogels comprised of DEX-lactate-HEMA (page 114) with dextran meeting the hydrophilic segment of claims 1, 6; the lactate meeting the hydrophobic segment of claims 1, 4; the HEMA meeting the smart segment of claims 1 and 9, one polymer smart segment can be used in place of the other, in

this case, poly(n-isopropylacrylamide) in place of the HEMA for the anticipated controlled release of protein pharmaceuticals.

18. Declaration under 37 CFR 1.132 by Tao Lu Lowe:

19. The declaration under 37 CFR 1.132 filed 06/10/09 is insufficient to overcome the rejection of claims 1, 2, 4-6, 8, 9 and 16-24 based upon 35 USC 103 over Hennink et al. (WO 98/00170) in view of Park et al. (US 6,271,278) or Hennink et al. (US 6,303,148) and over Bos et al., "Hydrogels for the Controlled Release of Pharmaceutical Proteins," in Pharmaceutical Technology, October, 2001, pp 110, 112, 114, 116, 118, 120 as set forth in the last Office action because:

20. a) The declarant's opinion that the ordinary artisan would not have found it obvious to replace HEMA in Hennink '170 with the N-isopropylacrylamide (NIPAAM) of Hennink '148 or Park is not persuasive because both HEMA and NIPAAM are known smart polymers so that one can substitute one smart polymer for the other and reasonably expect the polymer to effectively provide controlled delivery of drugs.

21. b) The declarant's opinion that the ordinary skilled artisan would not have found it obvious to achieve the present polymeric composition based on the disclosure of Bos is not persuasive because Bos specifically identifies poly(n-isopropylacrylamide) (NIPAAM) and methacrylates as responsive polymers (page 112, under hydrogel materials and also under abbreviations) with HEMA being a methacrylate. Also, Bos specifically mentions modified hydrogels comprised of DEX-lactate-HEMA (page 114) with dextran meeting the hydrophilic segment of claims 1, 6; the lactate meeting the hydrophobic segment of claims 1, 4; the HEMA meeting the smart segment of claims 1 and 9, and one smart polymer segment can be used in

place of the other, in this case, poly(n-isopropylacrylamide) in place of the HEMA for the anticipated controlled release of protein pharmaceuticals. The polymer of Bos is also capable of achieving the unexpected result proposed in paragraph 4 of the declaration.

22. c) The declarant states that the polymeric material having NIPAAM-dextran derivative released BSA within 15 days and over at 37 °C shown in instant Fig. 10, while HEMA-Dextran of Hennink, Fig. 5, released IgG in 6 days maximum at 37 °C contrary to the expectation that higher molecular weight molecules such as IgG would have longer release times over smaller molecules such as BSA. The examiner disagrees with the declarant's characterization of Fig. 5 of the Hennink and Fig. 10 of the instant application. First, the polymer of Fig. 10 is a NIPAAM-co-Dex-lactateHEMA (see paragraph [020], page 5 of the instant specification) and this polymer is not of the same scope as the claimed generic polymer of claim 1. Second, the opinion does not present any factual showing that NIPAAM cannot be used in place of HEMA. Third, Henning teaches that release rates of compounds in dextran hydrogels can be controlled by adjusting the water content and/or the degree of cross-linking, the degree of substitution, the number and length of hydrolysable groups in the spacer, the choice of hydrolysable spacers (see page 7, lines 5-9 ; page 11, lines 24-35 of Hennink). Specifically, lines 31-35 states that glycolic acid based spacers are hydrolytically more sensitive than spacers based on lactic acids; Hennink teaches that one can obtain dissolution times of from about 1 day to about 3 months or longer by varying the initial water content and the DS of the hydrogel (see page 10, lines 1-11 of Hennink); Hennink teaches that the manner in which the macromolecule is loaded on to the gel influences the loading capacity and hence the release profile. For example, burst release is obtained when the macromolecule adheres to the outside surface of the hydrogel (see page 10,

lines 18-25 of Hennink); Hennink teaches that the rate of release depends on the size of the hydrogel particles (see page 12, lines 4-7 of Hennink); Contrary to the hydrogel system, the rate of release from dextran hydrogels does not depend on the length of the water soluble polymers (see page 12, lines 8-12 of Hennink); such that taken the teachings of Hennink, it would be expected that the hydrogel can be easily tailored "with respect to protein drug release kinetics" ((see page 9, lines 24-30 of Hennink) to obtain desired release rates. Therefore, contrary to the declarant's opinion, one having ordinary skill in the art would tailor the hydrogel to achieve the desired release of protein drugs as suggested by Hennink not expecting that the release rate would be longer for larger molecules than smaller molecules. Fourth, the instant claim contemplates the use of the polymer of claim 1 for delivery of many drugs such as proteins, peptides, DNA, RNA, etc according to claims 18 and 19. For example, proteins are larger molecules than methylene blue. The declaration has not addressed what the release rates would be for most if not all of the molecules larger than BSA or smaller than BSA that are recited in claim 19 the polymer in Fig. 10 of the instant specification. Fifth, instant Fig. 10 is not commensurate in scope with claim 1 that does not contain biologically active molecule. Sixth, Hennink provides the evidence that release of compounds from dextran hydrogel is dependent on many factors enumerated above as DS, the initial water content, the size of the hydrogel particles and the manner in which the compounds are incorporated into the dextran hydrogel and not on one parameter such as molecular weight.

23. d) The example in Fig. 3 of the instant application is not commensurate in scope with claim 1 so that the statement in the declaration that the results of Fig. 3 is the result for the recited composition 1 is not persuasive. At best, the swelling data from Fig. 3 is the swelling

data of a polymer that has not been claimed since Fig. 3 is directed to PNIPAAM-PLLA-DEX having the various ratios listed on the Fig.

24. No claim is allowed.

25. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Blessing M. Fubara/
Examiner, Art Unit 1618